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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/854,326	05/11/2001	Toni Rita Prezant	18810-81401	7808

7590 01/09/2003

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	PAPER NUMBER
1632	12

DATE MAILED: 01/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/854,326	Applicant(s) Prezant et al.
	Examiner Shin-Lin Chen	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Nov 12, 2002 .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-10 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1-10 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 7 & 9
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's election without traverse of group I, claims 1-10, in Paper No. 11 is acknowledged.

2. Claims 11-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in Paper No. 11.

Applicants' amendment filed 11-12-02 has been entered. Claims 11-23 have been canceled. Claims 1-10 are pending and under consideration.

Priority

3. If applicant desires priority under 35 U.S.C. 120 or 119(e) based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the **first sentence** of the specification following the title, preferably as a separate paragraph. The reference regarding the claimed priority is in the second paragraph rather than appears as the first sentence (see specification, p. 1, lines 8-15). Appropriate correction is required.

4. Applicant's claim for domestic priority under 35 U.S.C. 119(e) and 120 is acknowledged. However, the provisional application 60/031,338 and applications 09/777,422, 09/730,469, 09/687,911, 09/569,956, 08/894,251 and PCT/US97/21463 fail to disclose the nucleotide sequence of SEQ ID No. 63 and the amino acid sequence of SEQ ID No. 64. Thus, the benefits

of the provisional application 60/031,338 and applications 09/777,422, 09/730,469, 09/687,911, 09/569,956, 08/894,251 and PCT/US97/21463 have been denied. The effective filing date of the present application is the actual filing date 5-11-01.

Claim Rejections - 35 USC § 101

5. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. Claim 9 is rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility.

The specification fails to provide an asserted use that meets the requirement of 35 U.S.C. 101 for inhibiting neoplastic cellular proliferation and/or transformation of a mammalian cell *in vitro*. There is no evidence of record for a well-established utility for inhibiting neoplastic cellular proliferation and/or transformation of a mammalian cell *in vitro*. There is no specific utility or a well-established utility for the mammalian cells whose neoplastic cellular proliferation and/or transformation has been inhibited. The only readily apparent use for the method is to study the effects of the method. The use of an invention as an object of further research or study does not meet the requirement of 35 U.S.C. 101.

Claim 9 is also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility

for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "and/or" in claims 1-3 is vague and renders the claims indefinite. It is unclear what is intended to be claimed. Changing the term "and/or" to "...or...or both" would be remedial. Claims 4-10 depend on claim 1 but fail to clarify the indefiniteness.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-8 and 10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inducing neoplastic transformation by PTTG1 polypeptide

and the proline-rich domain of PTTG1 is important for PTTG-mediated neoplastic transformation, and overexpression of PTTG2 inhibits transactivation activity of PTTG1 by nearly half *in vitro*, does not reasonably provide enablement for a method of inhibiting neoplastic cellular proliferation and/or transformation of a mammalian cell by delivering a composition comprising any expression vector expressing a mammalian PTTG2 peptide to a mammalian cell via any administration route *in vivo*, wherein said PTTG2 peptide consists essentially of amino acid residues 1-191 of SEQ ID No. 64 or a functional fragment thereof comprising at least 1-180 of SEQ ID No. 64, or a mammalian PTTG2 peptide having at least 95% identity to the PTTG peptide set forth above. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-8 and 10 are directed to a method of inhibiting neoplastic cellular proliferation and/or transformation of a mammalian cell, such as a malignant cell, by delivering a composition comprising an expression vector expressing a mammalian PTTG2 peptide to a mammalian cell *in vitro or in vivo*, wherein said PTTG2 peptide consists essentially of amino acid residues 1-191 of SEQ ID No. 64 or a functional fragment thereof comprising at least 1-180 of SEQ ID No. 64, or a mammalian PTTG2 peptide having at least 95% identity to the PTTG peptide set forth above, and said expression vector is complexed with a cellular uptake-enhancing agent.

The specification discloses that stable expression of human PTTG1 polypeptide in transfected NIH3T3 cells induces tumor formation *in vitro* and *in vivo*, and the proline-rich

domain of PTTG is important for PTTG-mediated neoplastic transformation. Human PTTG2 polypeptide is 90% identical to human PTTG1 polypeptide for 179 amino acid residues and its carboxyl terminal is non-homologous for an additional 12 amino acid residues, and removal of the carboxy terminal segment increases transactivation activity by 26 folds. The specification also discloses that overexpression of PTTG2 inhibits transactivation activity of PTTG1 by nearly half *in vitro* (specification, page 116). The claims encompass inhibiting neoplastic cellular proliferation and/or transformation of a mammalian cell by delivering a composition comprising any expression vector expressing the claimed mammalian PTTG2 peptide to a mammalian cell via any administration route *in vivo*.

The specification fails to provide adequate guidance and evidence for a method of inhibiting neoplastic cellular proliferation and/or transformation of a mammalian cell by delivering a composition comprising any expression vector expressing the claimed mammalian PTTG2 peptide to a mammalian cell via any administration route *in vivo* such that therapeutic effect can be obtained in a subject.

The claims read on gene therapy *in vivo*. The state of the art for gene therapy was unpredictable at the time of the invention. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of

cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Verma states that "The Achilles heel of gene therapy is gene delivery, and this is the aspect that we will concentrate on here. Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression...The use of viruses (viral vectors) is powerful technique, because many of them have evolved a specific machinery to deliver DNA to cells, However, humans have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses." (e.g. p. 239, column 3).

Further, Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of

degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy (e.g. bridging pages 81-82). In addition, Gorecki, 2001 (Expert Opin. Emerging Drugs, 6(2): 187-198) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g. abstract). In view of the lack of adequate guidance and evidence and the unpredictability in gene transfer as discussed above, one skilled in the art at the time of the invention would not know how to use various vectors comprising the polynucleotide encoding the claimed mammalian PTTG 2 peptide to inhibit neoplastic cellular proliferation and/or transformation of a mammalian cell via any administration route *in vivo* so as to provide therapeutic effect in a subject.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.

S L Chen